Maternal Medicine

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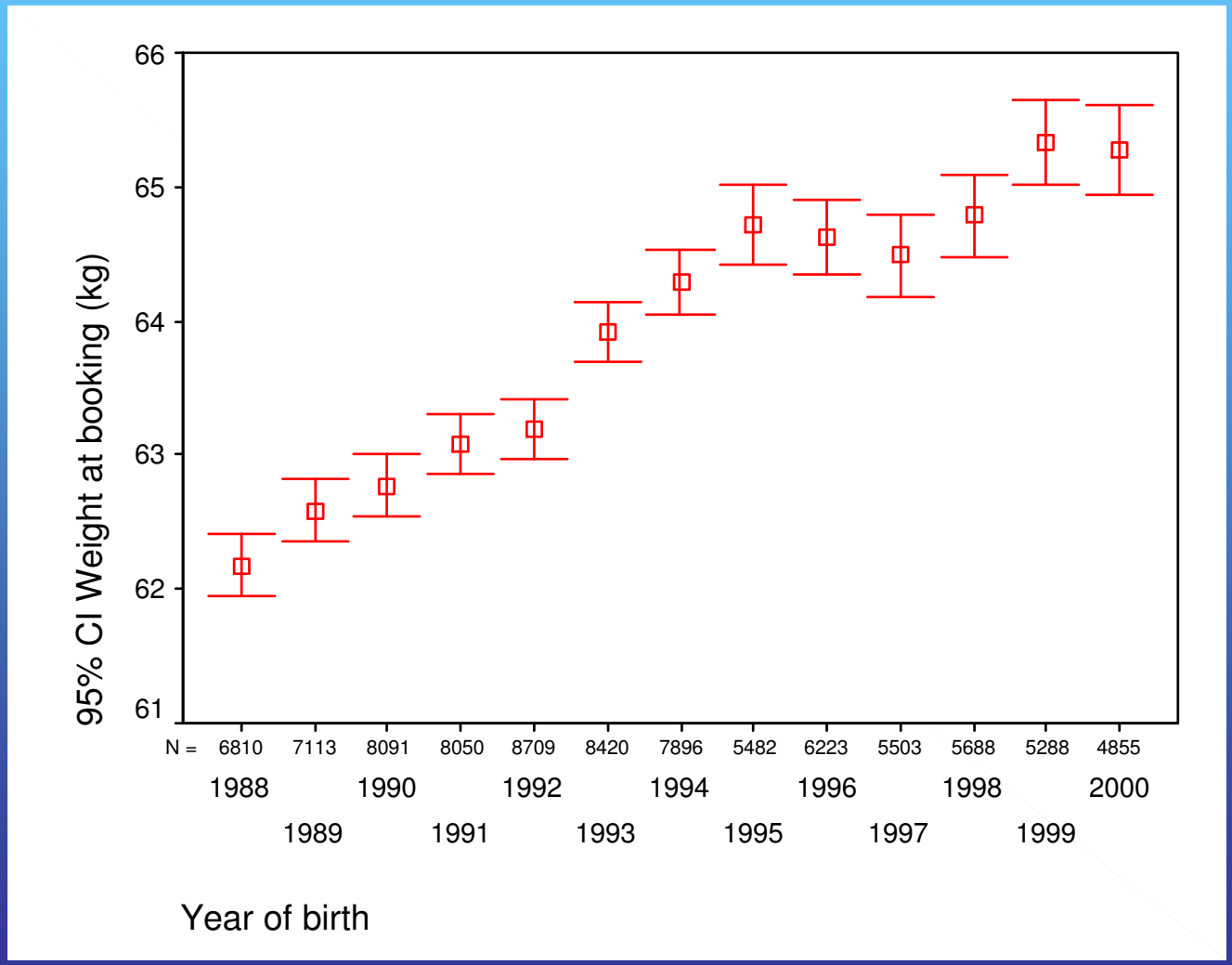
Introduction

- CEMACH
- Cardiac Disease
- Obesity
- Venous Thromboembolic Disease
- Pre-eclampsia
- Hypertension
- Diabetes
- Thyroid Disease
- Epilepsy

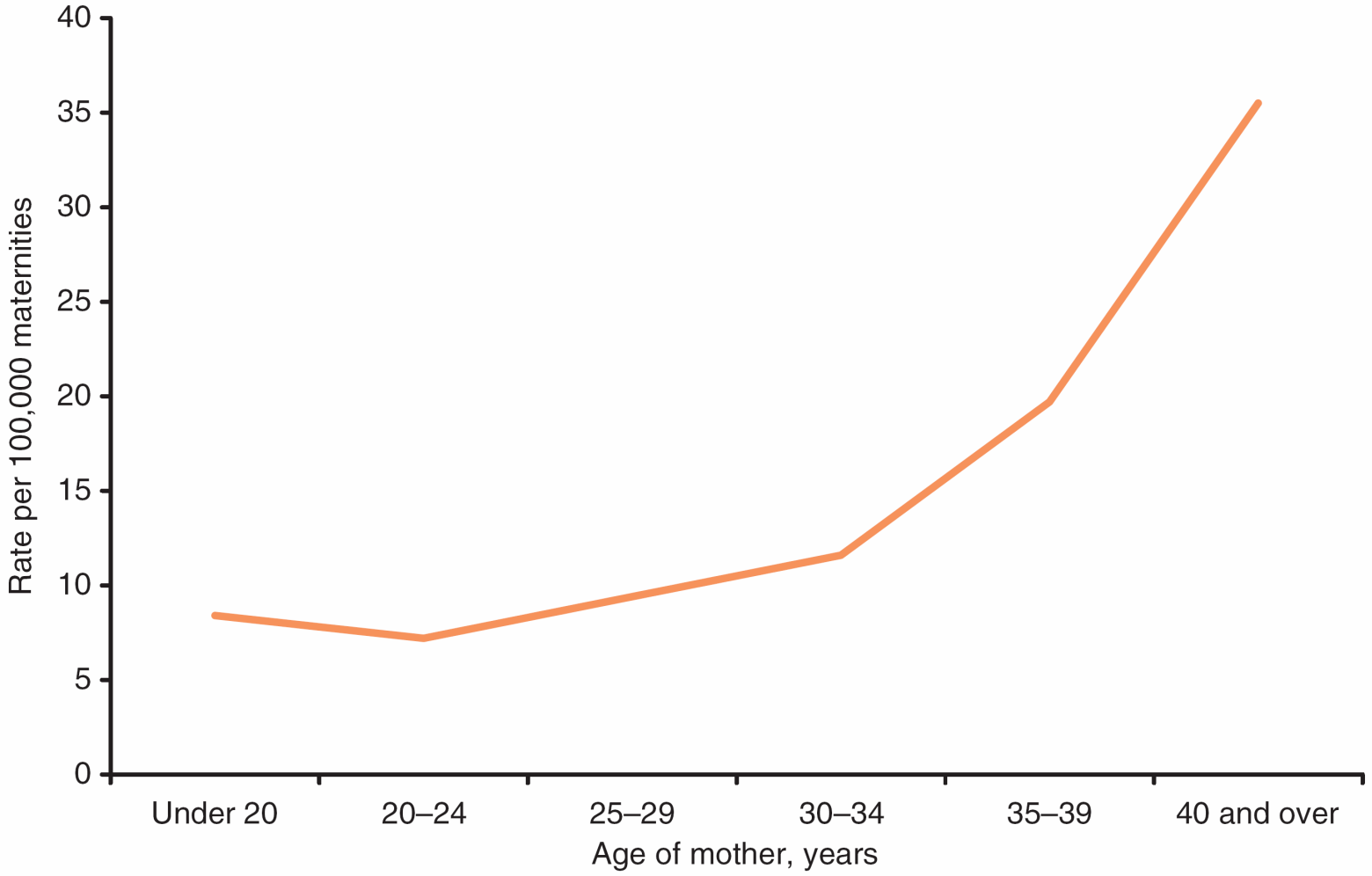
CEMACH 2003-2005 – the headlines

- Mortality rates have levelled off
  - Direct deaths
  - Indirect deaths
- High proportion of:
  - Obese patients (BMI>25 in 50%)
  - Socially deprived/late bookers/migrant population

Booking weight of 500,000 women in west London over 12 years

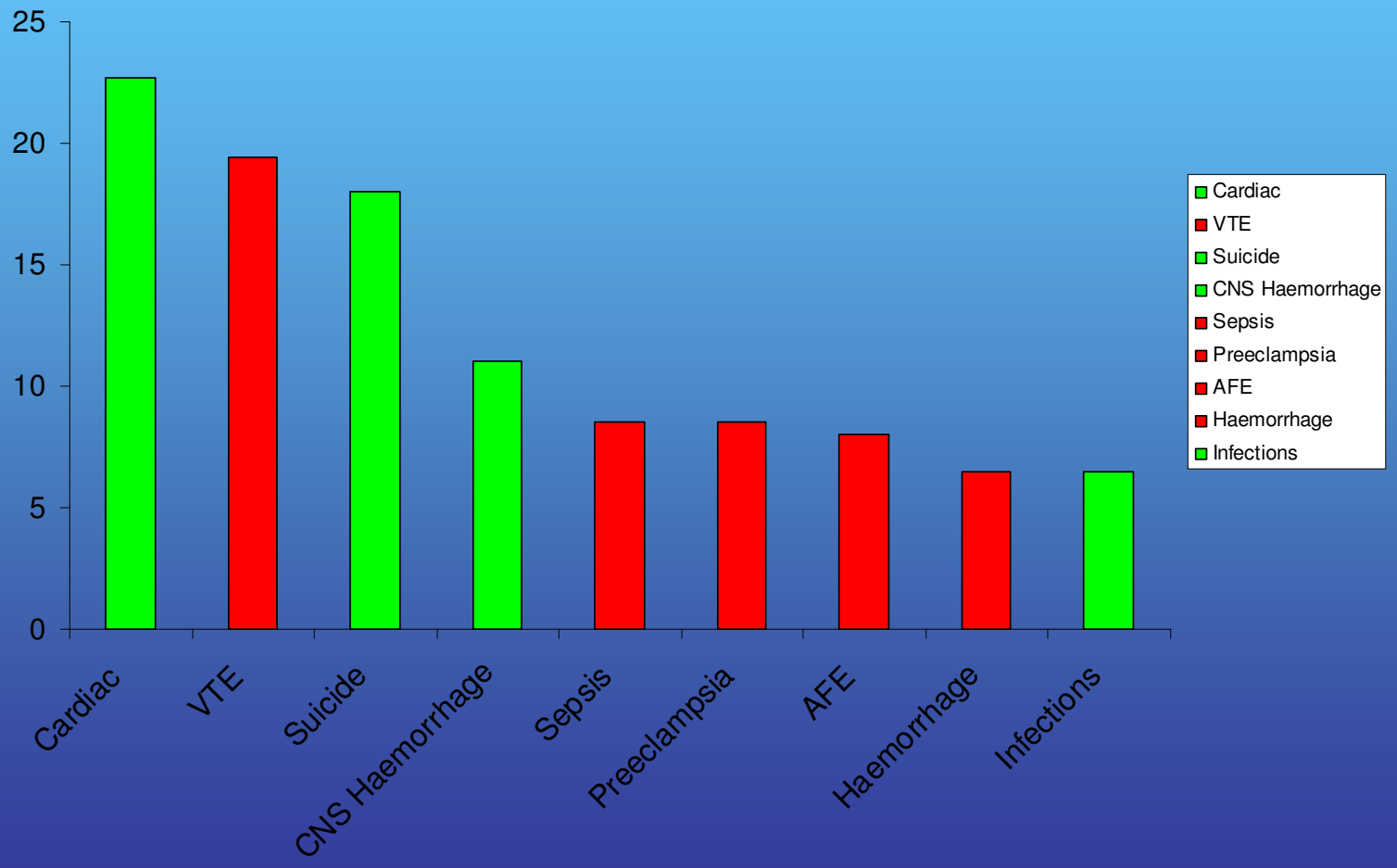


Age as a risk factor for maternal mortality

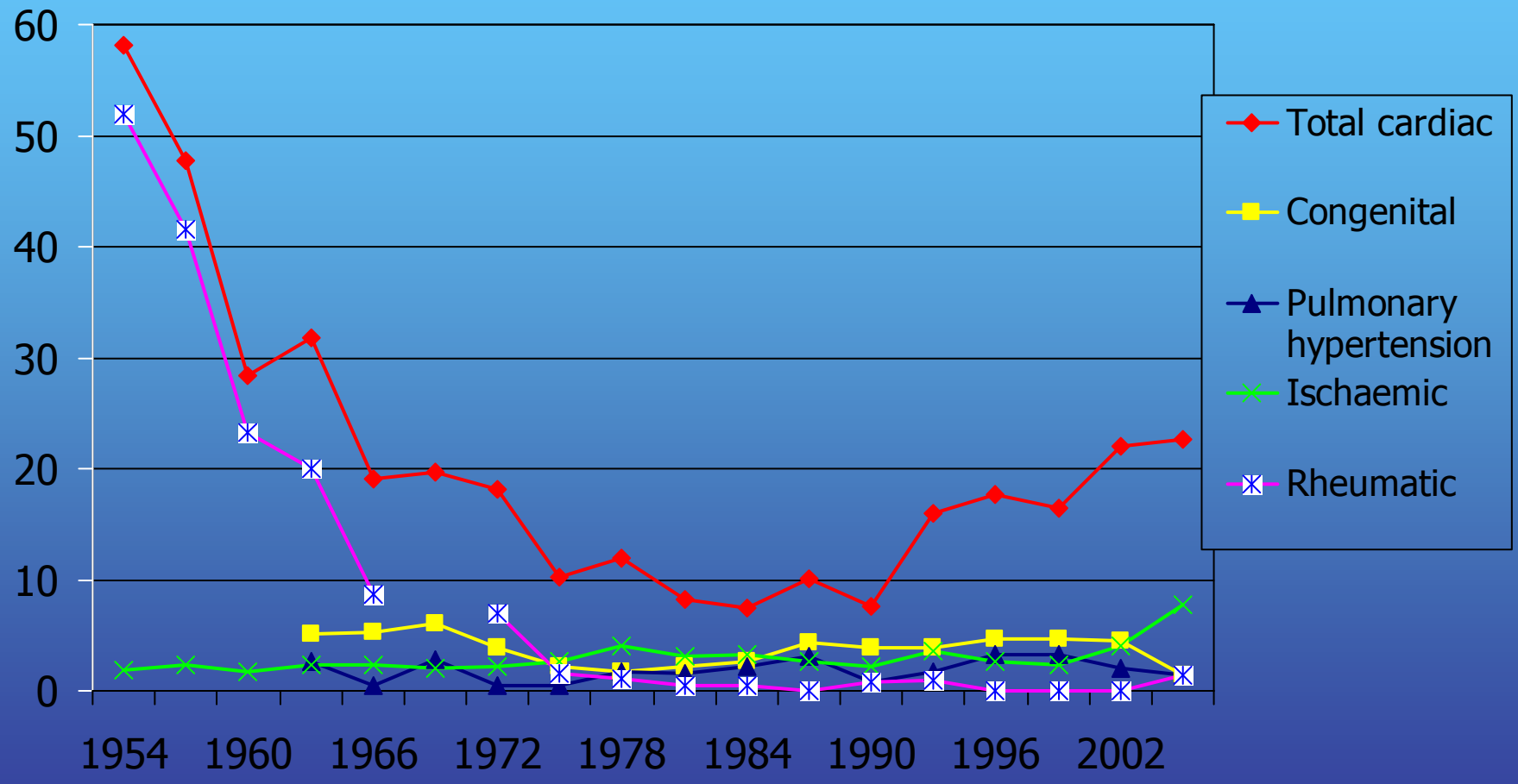


.8 Maternal mortality rate, *Direct* and *Indirect* deaths, by maternal age; United Kingdom 1985–02

Overall rates per million maternities CEMACH UK 2003-05

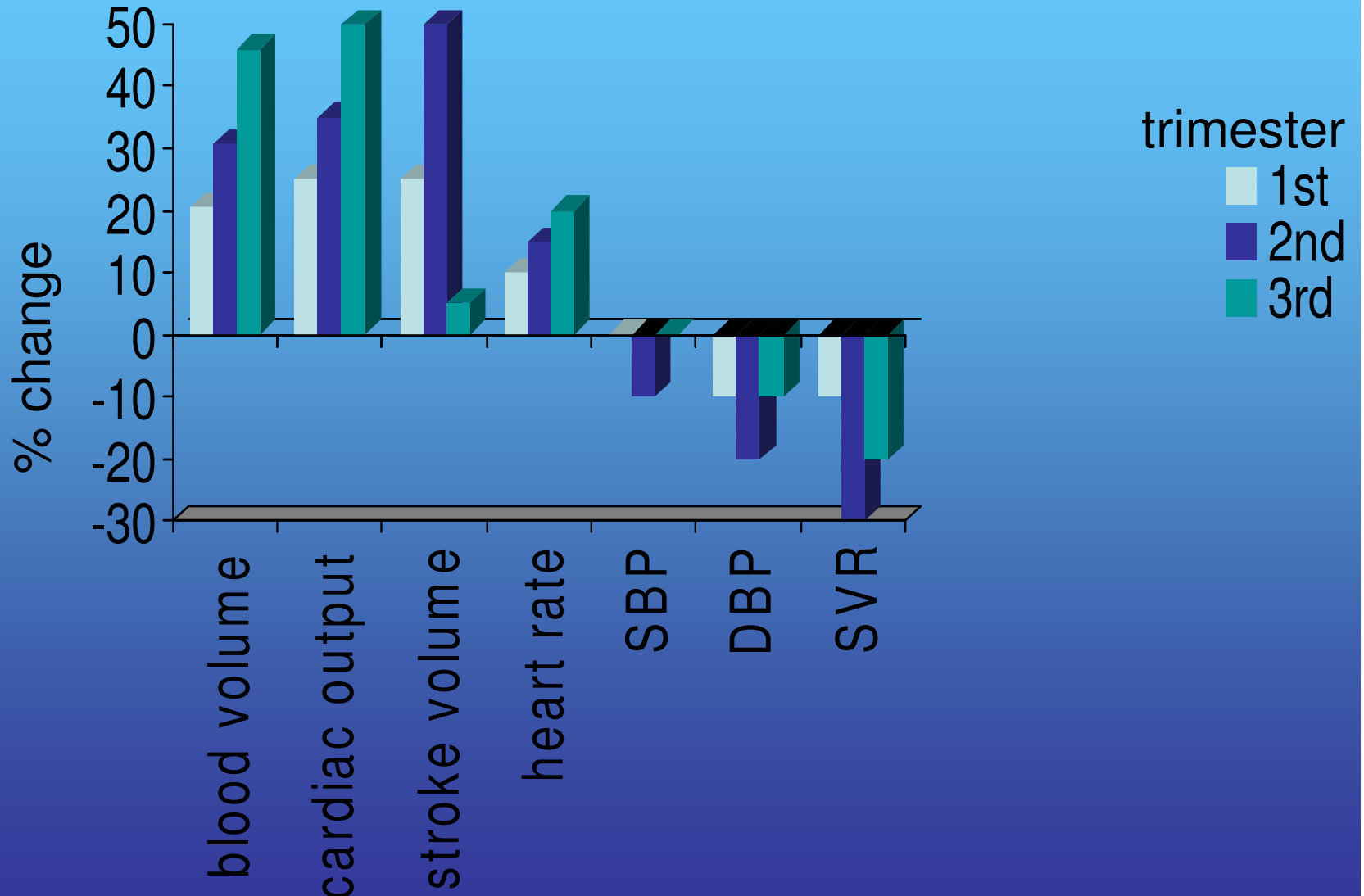


Cardiac causes (per million maternities) maternal mortality 1952-2005



Confidential Enquiry into Maternal and Child Health: Saving Mothers' Lives

Haemodynamic changes in Pregnancy



Cardiac deaths – the physiology

- Poorer prognosis with:
- Inability to increase the CO:
  - Stenotic lesions
  - Left ventricular failure
- Unable to accommodate increased venous return at delivery
  - Pulmonary Hypertension
- Increased pulse pressure/vascular wall sheer stress
  - Aortic dissection

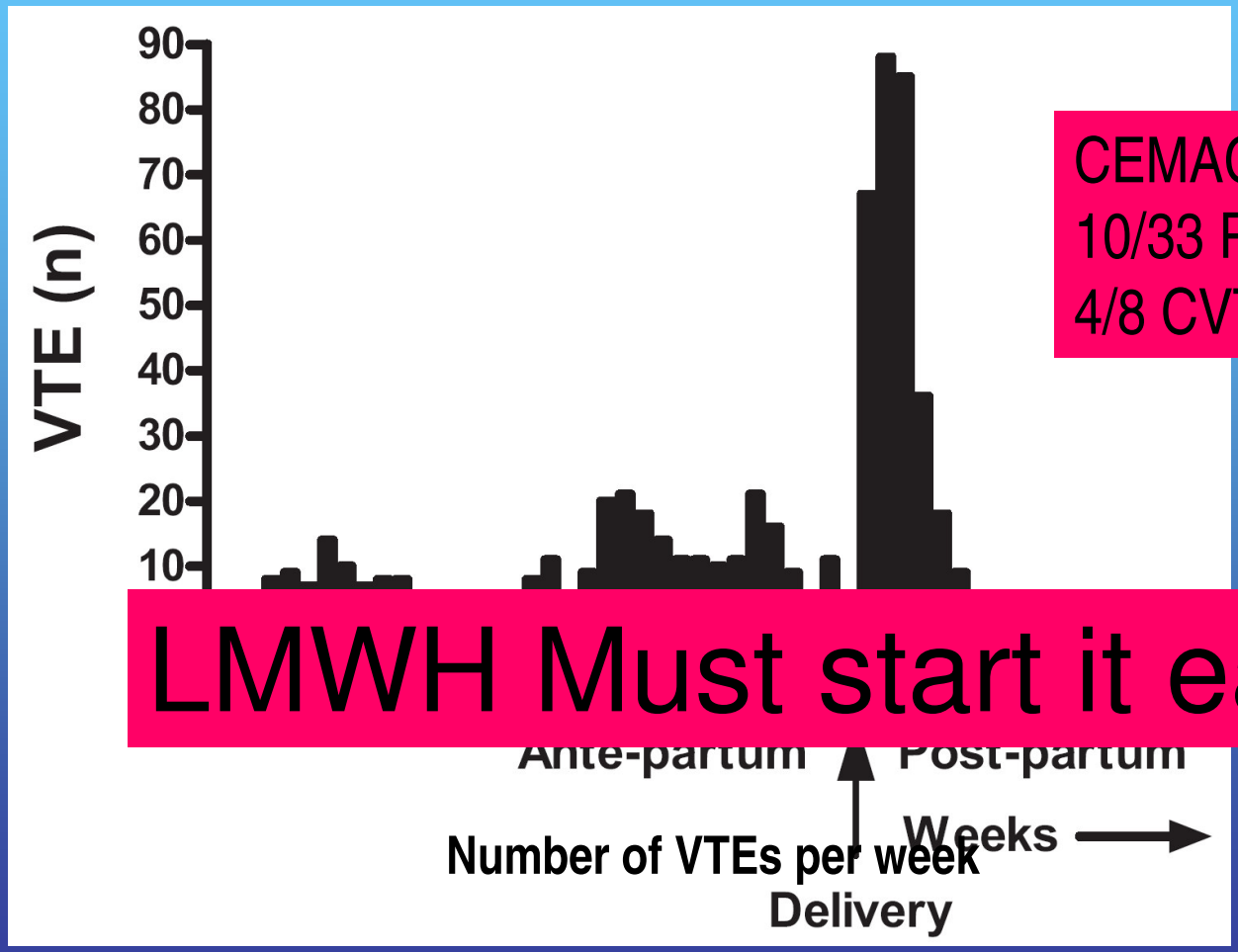
Venous Thromboembolism

- LEADING CAUSE OF DIRECT DEATH
- PREVENTABLE!
  - UKOSS PEs, 7 deaths – 73% ≥ 1 risk factors
  - CEMACH (PEs/CVTs)– 75% ≥ 1 risk factors

- LMWH does not cross placenta
- UFH versus LMWH
- Anti-Xa levels should be checked 2-4 weekly if on therapeutic dose
- Anti-Xa levels not required for thromboprophylaxis dosing
- NO evidence for the use of aspirin for thromboprophylaxis

- American College of Chest Physicians
- RCOG

Distribution of VTE in pregnancy and puerperium



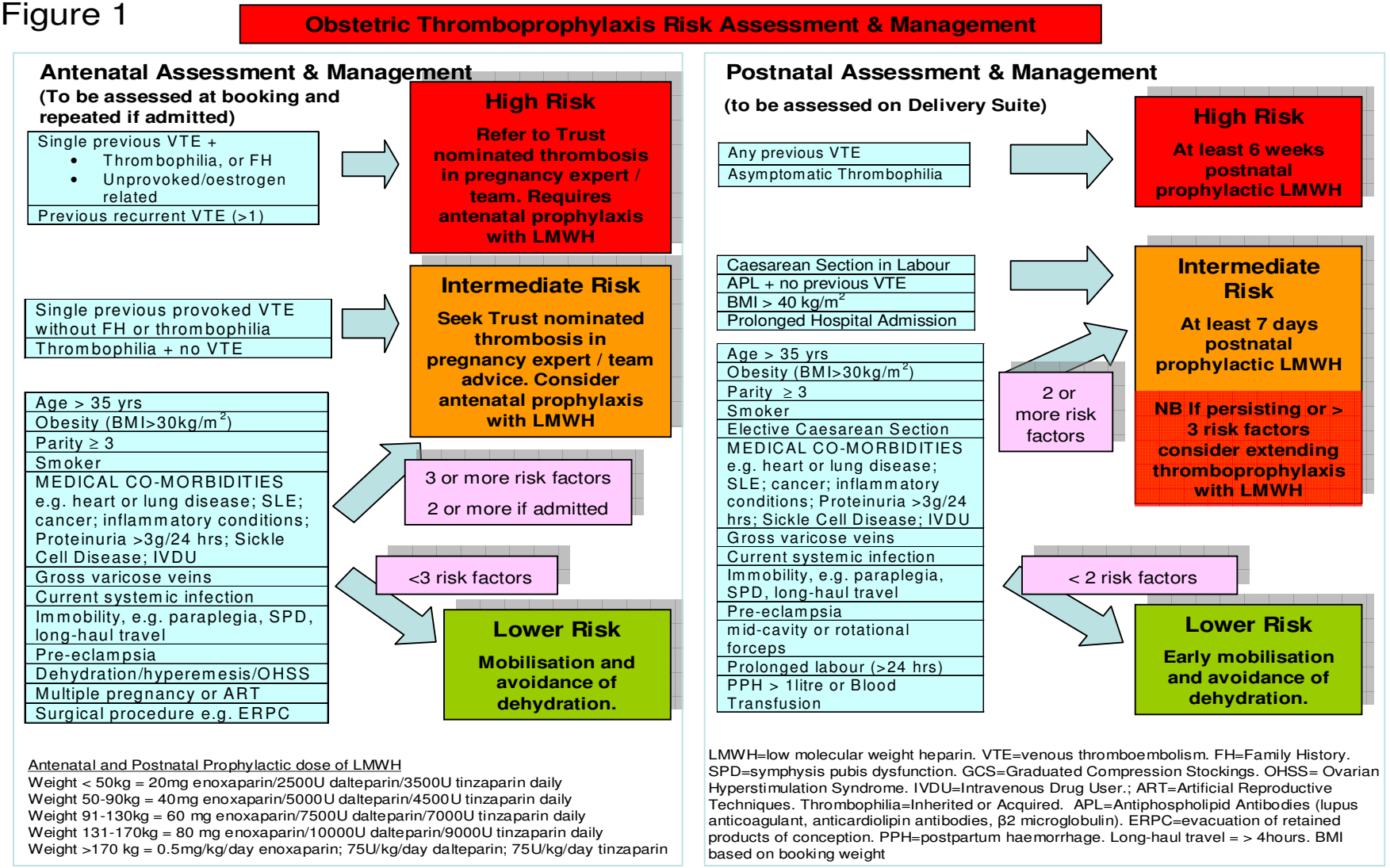
CEMACH
10/33 PEs in 1st trimester
4/8 CVTs in 1st trimester

LMWH Must start it early

Jaceobsen AF et al. AJOG. 2008;198: e223-7

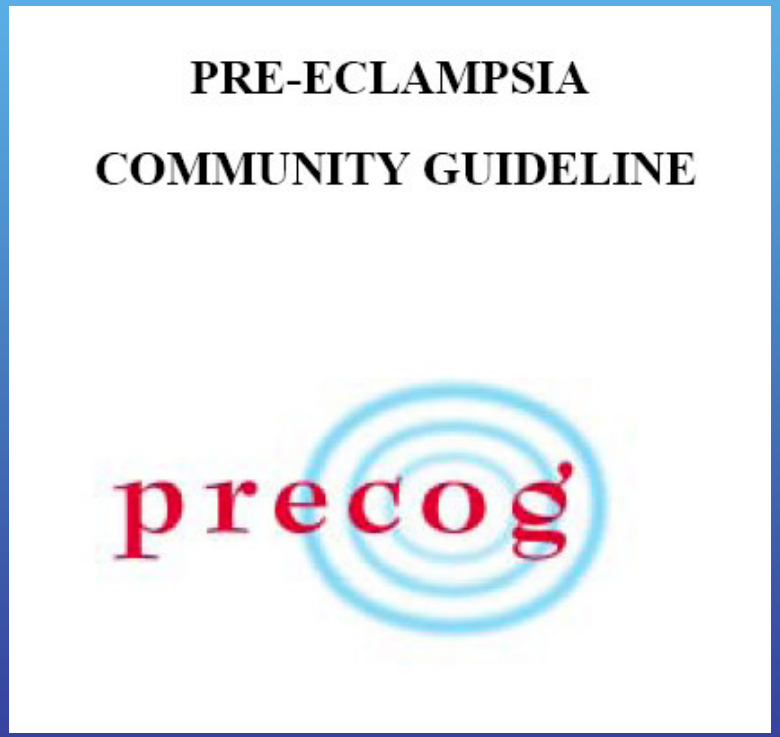
RCOG thromboprophylaxis guidelines 2009

Figure 1



Pre-eclampsia

- PRECOG guidelines



Pre-eclampsia – who gets it?

Table 1 The Strength of the Association of Selected Risk Factors for Preeclampsia*

Risk Factor Associated with Preeclampisa	Reference	OR (95% CI)
Preeclampsia in a previous pregnancy	Hnat[18]	3.88 (2.98-5.05)
	Duckitt[48]	7.19 (5.85-8.83)
First pregnancy	Conde-Agudelo[49]	2.38 (2.28-2.49)
	Duckitt[48]	2.91 (1.28-6.61)
Multifetal gestation	Sibai[50]	2.62 (2.03-3.38)
	Conde-Agudelo[49]	2.10 (1.90-2.32)
Chronic		21)
Gestati		22)
Pregest		25)
Vascula		99)
Nephropathy		3)
Urinary tract infection	Abi-Said[52]	4.23 (1.27-14.06)
Antiphospholipid antibody syndrome	Robertson[53]	2.73 (1.65-4.51)
	Duckitt[48]	9.72 (4.34-21.75)
Genetic factors (eg, thrombophilias)	Robertson[53]	
Factor V Leiden heterozygosity		2.19 (1.46-3.27)
Prothrombin heterozygosity		2.54 (1.52-4.23)
MTHFR homozygosity		1.37 (1.07-1.76)
Hyperhomocysteinemia		3.49 (1.21-10.11)
Obesity (BMI >35 kg/m^2)	Sibai[1]	3.38 (1.91-6.00)
Maternal age >35 years	Conde-Agudelo[49]	1.67 (1.58-1.77)
Family history of preeclampsia	Duckitt[48]	2.90 (1.70-4.93)
Fetal malformation	Conde-Agudelo[49]	1.26 (1.16-1.37)
Abnormal maternal serum markers (AFP, hCG, uE3, Inhibin A)	Dugoff[54]	
Inhibin A >2.0 MOM		2.39 (1.75-3.26)
2 abnormal markers		3.65 (2.79-4.78)
African-American race	Tucker[55]	1.2 (0.8-1.7)

Abbreviations: AFP, alpha fetoprotein; HCG, human chorionic gonadotropin; uE3, unconjugated estriol.
*Presented as odds ratio (OR) and 95% confidence intervals (CI).

OR~30 for renal disease especially if renal impairment and/or significant proteinuria

Gary A et al. Sem in Perinatol. 2007;31:135-141

Pre-eclampsia

Investigations after early onset PET

- DRVVT (lupus anticoagulant)
- Anti-Cardiolipin antibodies
- Full thrombophilia screen (FVL, PT gene mutation, anti-thrombin, Protein C&S)

Prophylaxis

- Vitamin C&E
- Calcium
- Aspirin
- ??± LMWH

Pre-eclampsia - recurrence

- "…pre-eclampsia, preterm birth, fetal growth restriction, placental abruption, and perinatal death, are considered to have overlapping etiologic mechanisms that related to abnormal placentation. Thus pregnancy with pre-eclampsia in an initial pregnancy appears to be a risk for these other pregnancy complications…."

Gary A et al. Sem in Perinatol. 2007;31:135-141

Pre-eclampsia- recurrence risk

- Depends on the study population!

Table 2 Summary of Studies that Present the Risk for Recurrence of Preeclampsia

Author	Study Population	Rate of Recurrence
Campbell[7]	Preeclampsia (n = 279)	Preeclampsia 7.5%
Sib[illegible]	[illegible]	[illegible]
var		
Su[illegible]		
Sib[illegible]		
		HELLP 3%
Chames[13]	HELLP with delivery <28 weeks (n = 62)	Preeclampsia 55%
		HELLP 6%
Adelusi[14]	Eclampsia (n = 64)	Eclampsia 16%
Sibai[16]	Eclampsia (n = 366)	Preeclampsia 22%
		Eclampsia 2%
Trogstad[17]	Preeclampsia singleton (n = 19,960)	Preeclampsia 14.1%
	Preeclampsia twins (n = 325)	Preeclampsia 6.8%

Recurrence risk anywhere between 7.5% and 75%!
Higher risk if early onset, associated with HELLP or Eclampsia
Risk of recurrent HELLP or eclampsia - low

Gary A et al. Sem in Perinatol. 2007;31:135-141

Pre-eclampsia and CVS disease

Systematic review and meta-analysis

After PET women have an increased risk of vascular disease but not cancer

Disease	Weighted mean f/up (yrs)	RR (95%CI)	Absolute risk at time of f/up (%)
Hypertension	14.1	3.7 (2.7 to 5.05)	21.9
Ischaemic Heart Disease	11.7	2.16 (1.86 to 2.25)	0.2
Stroke	10.4	1.81 (1.45 to 2.27)	0.2
VTE	4.7	1.79 (1.37 to 2.33)	0.3

Dose response relationship (severe BP, early onset PET)

Bellamy et al. BMJ. 2007;335:974-977

Cardiovascular System

- Healthy pregnancy mimics CVS disease
- Healthy pregnancy is a transient metabolic syndrome of
  - increased lipids,
  - Pro-inflammatory state
  - Pro-coagulant state
  - Insulin resistant state
  - High cardiac output
- This is a pro-atherogenic metabolic syndrome

CVD risk factors & Pre-Eclampsia

- 3494 women, 133 (3.8%) had PET
- Adjusted for smoking, previous PET, parity, maternal age, education, socioeconomic position, time between baseline and delivery

- Increased incidence of:
  - higher waist circumference comparing <67cm & >83cm (OR=2.2,95%CI 1.2-3.8)
  - Systolic BP comparing BP< 111mmHg & > 130mmHg (OR=7.3, 95%CI 3.1-17.2)
  - Diastolic BP comparing <64mmHg & > 78mmHg (OR=6.5, 95%CI 2.9-14.6)
  - Non-fasting total cholesterol

Magnussen et al. BMJ. 2007; 335:978-981

CVS disease and PET

- Women with pre-existing hypertension, obesity, high cholesterol are more likely to develop pre-eclampsia.
- Women who have had pre-eclampsia are more likely to develop CVS disease in later life.
- Rather than causative, PET and CVD may have a shared aetiology.

Magnitude of the risk for CVD in women with Hx PET is similar to dyslipidaemia

Hypertension

- Investigate for secondary causes
- In pregnancy
  - Renal USS
  - Ca/ TFTs/Na/K/Cr
  - ECG

Hypertension – treatment in pregnancy

Agent	Receptor	Dose Range	Side Effects	Contra-indications
Methyl-dopa	Central action	250mg – 3 g tds	GI disturbance, dry mouth, headache, dizziness, low mood, sedation, stomatitis, bradycardia	Liver disease, depression, pheo-chromocytoma
Nifedipine	Calcium Channel antagonist	20-90mg od SR or 10-40mg bd MR	Headache, flushing, dizziness, lethargy, tachycardia, palpitations, ankle oedema, rash, nausea, visual disturbance	Aortic stenosis, Aortic Coarctation, Liver disease
Labetalol	α- and β-adrenoreceptors	200-1600mg tds	Bradycardia, brochospasm, GI disturbance, fatigue, scalp tingling	Asthma, pheo-chromocytoma

Hypertension – treatment in pregnancy

- I also use Amlodipine

- ACEI/ARBs – fetotoxic and embryotoxic
- Stop pre-preg or at confirmation of conception (e.g. diabetic nephropathy)

- Atenolol is associated with IUGR

Gestational Diabetes

Australian Carbohydrate Intolerance Study (ACHOIS)

- Large multi-centre RCT
- Diagnosis
  - Fasting BM < 7.8 mmol.L
  - 2 hrs after 75g OCTT – 7.8 -11.0 mmol/L

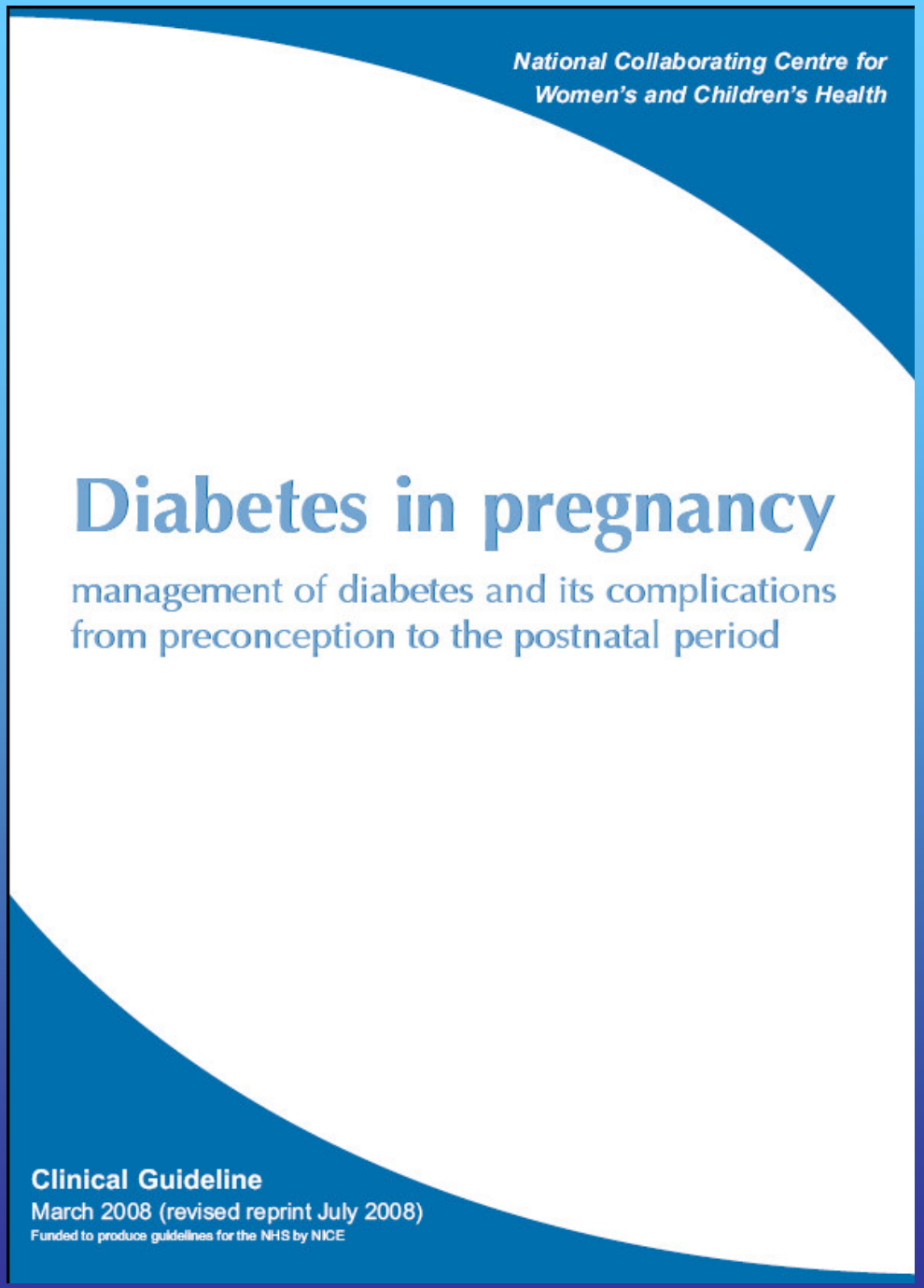
- Rate of serious perinatal complications was significantly lower in intervention group
- Women in intervention group had higher rates of IOL + neonatal nursery admissions but not CS

Crowther et al. NEJM;352:2477-2486, 2005

Importance of Pre-pregnancy counselling

- Diet/exercise/Weight loss measures
- Aim for HbA1C <7 pre-preg
- Folic Acid 5 mg od from 3 months pre-preg
- Retinal and renal assessment
- Review medications/change in preparation for pregnancy

New care pathway will be out for consultation soon



Gestational Diabetes

- Recurrence risk – 35-70%
  - Increasing parity
  - BMI> 30
  - Diagnosis <24 weeks
  - Requiring insulin

Joseph & Bottalico. Sem perinatol. 2007:176-184

- Long-term risk of diabetes
  - ~ 10% of patients have diabetes soon after delivery
  - ~ 70% on long-term follow-up (>10 years)

Buchanan & Xiang. J Clin Invest. 2005;115:485-491

- Importance of OGTT 6/52 postnatal

Thyroid disease

- Silver star referral if poorly controlled hypothyroid disease or any one with hyperthyroid or previous Graves.

- If stable hypothyroid – keep TSH at low end of normal (non-pregnant) range.
- If appropriately replaced at conception, dose unlikely to need to be increased.

Epilepsy

- All anti-convulsants are teratogenic
- Background risk of congenital malformations - ~3%
- 1 drug - ~ 7%
- 2 drugs - ~15%
- Evidence of dose dependence

- Carbemazipine probably safest but not good for generalised epilepsy
- Valproate – worst safety profile, in addition evidence of neuro-developmental delay in offspring

Epilepsy

- HOWEVER
- Almost always – benefit of staying on anti-convulsant outweighs risk.

- Aim for as few drugs as possible, and on the lowest dose possible
- Pre-pregnancy counselling
- Folic Acid 5 mg
- Referral to Silver Star for increased maternal and fetal surveillance

High dose - Folic Acid (5mg)

- Any one on anti-convulsants
- All diabetics (type 1 and 2)
- Sickle Cell (Hb SS, Hb SC)
- Those taking methotrexate within the last 6 months
- Those taking sulphasalazine
- Terminal ileal disease e.g. Crohn's or Coeliac
- Those with demonstrated deficiency

Breastfeeding

Generally

- Little evidence
- Most drugs are excreted in breast milk
- However, this equates to a fraction of the dose in the neonate
- Benefit > Risk

- OK – Warfarin, LMWH, aspirin, ACEI (Captopril/Enalapril), Oxypreolol/Atenolol, Nifedipine/Amlodpine. Low dose Prednisolone
- Caution but probably OK – Azathioprine, Tacrolimus, High dose Prednisolone
- Not enough evidence yet - biologics

Maternal Medicine Clinics

- General Pre-pregnancy clinic (Women's Centre - Lucy Mackillop)
- Joint Obstetric Medicine/Cardiology Clinic (Women's Centre - Lucy Mackillop/Oliver Ormerod)
- Joint Psychiatry/Obstetric Clinic (Women's Centre - Anita Makins/IPPS)
- Diabetes (Jonathan Levy – OCDEM)
- Post-natal clinic (Women's Centre - Lucy Mackillop)

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Pre-pregnancy counselling

- **Hypertensive disorders**, pre-existing hypertension, previous eclampsia/pre-eclampsia or HELLP syndrome
- **Cardiac**, e.g. valvular disease, congenital heart disease, arrthymias, cardiomyopathy, ischaemic heart disease
- **Renal**, e.g. chronic renal failure of any cause, renal transplant, reflux nephritis
- **Respiratory**, e.g. asthma, cystic fibrosis, sarcoidosis
- **Rheumatological/Connective tissue disease**, e.g. rheumatoid arthritis, SLE, antiphospholipid syndrome, Marfan's syndrome, Ehlers Danlos syndrome
- **Hepatic**, e.g. viral hepatitis, primary biliary cirrhosis, primary sclerosing Cholangitis, previous obstetric cholestasis or acute fatty liver of pregnancy
- **Gastrointestinal**, e.g. inflammatory bowel disease, previous hyperemesis gravidarum.
- **Haematological,** e.g. venous thromboembolism, sickle cell disease, immune thrombocytopenic purpura, thombotic thrombocytopenic purpura, haemophilia
- **Endocrine**, e.g. diabetes with any other medical condition, thyroid disease, pituitary disease, parathyroid disease, adrenal disease
- **Neurological**, e.g. epilepsy, multiple sclerosis, migraines, cerebrovascular accident, myasthenia gravis, idiopathic/benign intracranial hypertension.
- **High BMI:** BMI> 40 or a BMI> 30 AND co-morbidities e.g. hypertension

Pre-pregnancy counselling

This is the key!

~60% of pregnancies are unplanned

PPC should be offered to every woman of childbearing age who has a co-existence medical condition.